

## Parental Education and Genetics of BMI from Infancy to Old Age : A Pooled Analysis of 29 Twin Cohorts

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# Parental Education and Genetics of BMI from Infancy to Old Age: A Pooled Analysis of 29 Twin Cohorts

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**Objective:** The objective of this study was to analyze how parental education modifies the genetic and environmental variances of BMI from infancy to old age in three geographic-cultural regions.

**Methods:** A pooled sample of 29 cohorts including 143,499 twin individuals with information on parental education and BMI from age 1 to 79 years (299,201 BMI measures) was analyzed by genetic twin modeling.

**Results:** Until 4 years of age, parental education was not consistently associated with BMI. Thereafter, higher parental education level was associated with lower BMI in males and females. Total and additive genetic variances of BMI were smaller in the offspring of highly educated parents than in those whose parents had low education levels. Especially in North American and Australian children, environmental factors shared by co-twins also contributed to the higher BMI variation in the low education level category. In Europe and East Asia, the associations of parental education with mean BMI and BMI variance were weaker than in North America and Australia.

**Conclusions:** Lower parental education level is associated with higher mean BMI and larger genetic variance of BMI after early childhood, especially in the obesogenic macro-environment. The interplay among genetic predisposition, childhood social environment, and macro-social context is important for socioeconomic differences in BMI.

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## Introduction

Mean body mass index (BMI; in kilograms per meter squared) has increased all over the industrialized world during the past four decades and currently shows clear geographic differences, with the highest BMIs in North America and the lowest BMIs in East Asia (1). Twin studies have shown that genetic factors explain a substantial proportion

of BMI variation over the life course (2,3), and genome-wide association (GWA) studies have identified the role of genetic variants behind BMI variation (4,5). There is also strong evidence for higher BMI in lower socioeconomic classes in Western industrialized societies (6). The roots of socioeconomic obesity differences may already emerge in childhood because many socioeconomic characteristics of the childhood family, such as parental education and income, are associated

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with the BMI of offspring (7). Adoption studies have supported these findings by showing that lower socioeconomic status of biologically unrelated adoptive families is associated with higher BMI of adopted children as adults (8).

The association of genes and environmental factors with BMI may be modified by sociodemographic characteristics. In our previous study based on the same database as this present study, we found that the genetic variation of adult BMI increased from the 1940s to the 2010s at the same time that mean BMI dramatically increased (3), confirming the earlier findings based on Danish (9) and Swedish data (10). A Dutch twin study of parental education in children and adolescents (11), as well as studies on education of Danish (12) and US adults (13), suggested increased genetic BMI variation associated with less education. However, a Finnish twin study reported that in adolescence, the increased BMI variation in the offspring of parents with less education was attributable to environmental factors shared by co-twins (14).

Addressing the question of how modification of genetic and environmental influences on BMI develops over the human life-span requires considerable statistical power. Thus, we analyzed whether and how parental education modifies the genetic and environmental variation of BMI from infancy to old age in a very large international database of twins. Further, we analyzed whether the interaction between parental education and BMI varies among three geographic-cultural regions that are characterized by different levels of mean BMI in the population, indicating different obesogenic environments.

## Methods

The data were derived from the Collaborative Project of Development of Anthropometrical Measures in Twins (CODATwins) targeted to collect all available twin data on height and weight in the world (15). We included 29 twin cohorts with additional information on maternal and paternal education. Eleven cohorts came from European countries, five cohorts came from East Asian countries, eleven cohorts came from the United States, and single cohorts came from Australia and Israel. The names of participating cohorts are given in Table 1 (legend). Age was classified into 1-year age categories from 1 to 19 years of age, and after that, 10-year categories were defined. Participants who were 80 years of age or older were excluded (319 measures) because of decreasing muscle mass at old age (16). Together, there were 324,329 BMI measurements. In children and adolescents, we checked the BMI distribution in each age and sex group and removed the extreme, likely erroneous values (658 measures representing 0.3% of the measurements at 19 years of age or younger corresponding to values approximately 3 SDs less than or greater than the mean). In adults, we removed the measurements consistent with anorexia nervosa (BMI < 15 kg/m<sup>2</sup>, 96 measures representing 0.1% of adult measures) and morbid obesity (BMI > 45 kg/m<sup>2</sup>, 246 measures representing 0.3% of adult measures). Thus, our results represent the range of normal BMI variation and do not represent extremely low and very high BMI values, which may be affected by specific factors such as anorexia nervosa or rare monogenic traits. To confirm that all parameter estimates were based on independent observations, we selected one measurement in each age group from cohorts with repeated measures and conducted independent models in each age group. In the present analyses, 299,201 BMI measures from 143,499 twin individuals (52% females) including 66,165 complete twin pairs (39% monozygotic [MZ], 34% same-sex dizygotic [DZ], and 27% opposite-sex DZ) with information on

maternal and paternal education were used. All participants were volunteers who gave informed consent when participating in their original studies. The pooled analysis was approved by the ethical committee of the Department of Public Health, University of Helsinki.

The different educational classifications used in the surveys were transformed as educational years, as described elsewhere (17). We first calculated regression residuals of maternal and paternal education separately by fitting a regression model with maternal or paternal education as the dependent variable and twin cohort and the birth year of their twin children, used as a proxy indicator for the birth years of parents, as independent variables. Twin cohort was treated as a nominal-level variable with a dummy variable for each individual cohort and birth year as a continuous variable. These residuals were then summed up to get combined parental education and divided into three categories (less than 0.5 SDs from the mean, from 0.5 to 0.5 SDs from the mean, and more than 0.5 SDs from the mean) to indicate low (31% of participants), average (40% of participants), and high parental education levels (29% of participants). The SD of parental education was slightly higher in North America and Australia (SD = 5.33) than in Europe (SD = 4.50) and East Asia (SD = 4.10). However, we calculated the residuals in the full cohort and used the same categorization of parental education to avoid changing the educational distribution and to confirm the same extent of education in all geographic-cultural regions. Thus, the residuals indicate how much shorter or longer the parental education duration is as compared with that of the average person having a certain birth year in each twin cohort. Correspondingly, BMI was adjusted for the effects of exact age and twin cohort in each age and sex category by regression models.

In the aggregation of twin cohorts by the geographic-cultural regions, we removed Turkey from all region-specific analyses because the Turkish population is genetically distinct from other European populations (18). We also combined the cohort from Australia with North American cohorts because the mean BMI in Australia is closer to that in North American than European countries (1). Thus, we had three geographic-cultural regions (North America and Australia, Europe, and East Asia) representing the high, intermediate, and low levels of obesogenic factors in the environment, respectively, based on the mean BMI of population (1). The same classification was also used in our previous studies on the genetics of BMI in childhood (2) and adulthood (3), which were based on the CODATwins database. The number of BMI measurements was highest in Europe (196,990 measures), followed by North America and Australia (82,098 measures) and East Asia (18,670 measures). Because there was more ethnic diversity in North America and Australia than in the other cultural-geographic regions, we repeated the main analyses in North Americans and Australians of Caucasian ethnicity based on self-reports (75,973 measures).

We used structural equation modeling to estimate genetic and environmental variance components (19). Genetic twin modeling is based on the different genetic relatedness of MZ and DZ twins: DZ twins share, on average, 50% of their genes (identical by descent); MZ twins are virtually identical at the DNA-sequence level. Based on this principle, the BMI variation can be decomposed into additive genetic variation (additive effects of all loci affecting BMI), dominance genetic variation (nonadditive genetic effects), shared environmental variation (all environmental effects making co-twins similar), and unique environmental variation (all environmental effects making co-twins different and measurement error). Models were fitted separately for each parental education category by age groups.

TABLE 1 Number of twin individuals with BMI and parental education by age

| Age   | Males  |                          |      |                        |      |                        |      | Females |                          |      |                        |      |                        |      |
|-------|--------|--------------------------|------|------------------------|------|------------------------|------|---------|--------------------------|------|------------------------|------|------------------------|------|
|       | N      | BMI (kg/m <sup>2</sup> ) |      | Maternal education (y) |      | Paternal education (y) |      | N       | BMI (kg/m <sup>2</sup> ) |      | Maternal education (y) |      | Paternal education (y) |      |
|       |        | Mean                     | SD   | Mean                   | SD   | Mean                   | SD   |         | Mean                     | SD   | Mean                   | SD   | Mean                   | SD   |
| 1     | 13,548 | 17.1                     | 1.36 | 13.8                   | 2.31 | 13.9                   | 2.6  | 14,023  | 16.7                     | 1.37 | 13.8                   | 2.33 | 13.9                   | 2.63 |
| 2     | 11,273 | 16.5                     | 1.37 | 14.0                   | 2.42 | 14.0                   | 2.70 | 11,324  | 16.2                     | 1.37 | 14.0                   | 2.44 | 13.9                   | 2.76 |
| 3     | 10,907 | 15.9                     | 1.32 | 14.2                   | 2.49 | 14.2                   | 2.73 | 11,460  | 15.6                     | 1.37 | 14.2                   | 2.51 | 14.1                   | 2.76 |
| 4     | 3,533  | 15.9                     | 1.68 | 15.3                   | 3.39 | 14.7                   | 3.61 | 3,579   | 15.7                     | 1.68 | 15.4                   | 3.38 | 14.7                   | 3.68 |
| 5     | 6,533  | 15.3                     | 1.58 | 14.4                   | 2.61 | 14.3                   | 2.82 | 6,577   | 15.1                     | 1.66 | 14.3                   | 2.53 | 14.3                   | 2.84 |
| 6     | 1,898  | 15.7                     | 1.95 | 15.1                   | 3.07 | 14.9                   | 3.23 | 1,998   | 15.5                     | 1.98 | 15.2                   | 3.11 | 14.9                   | 3.32 |
| 7     | 7,084  | 15.4                     | 1.78 | 14.3                   | 2.44 | 14.3                   | 2.64 | 7,499   | 15.4                     | 1.94 | 14.2                   | 2.48 | 14.3                   | 2.71 |
| 8     | 4,388  | 15.8                     | 2.06 | 14.4                   | 2.80 | 14.3                   | 2.89 | 4,503   | 15.8                     | 2.22 | 14.4                   | 2.79 | 14.3                   | 2.95 |
| 9     | 3,497  | 16.7                     | 2.60 | 14.7                   | 3.14 | 14.4                   | 3.23 | 3,471   | 16.7                     | 2.76 | 14.8                   | 3.12 | 14.5                   | 3.28 |
| 10    | 7,017  | 16.6                     | 2.39 | 14.1                   | 2.57 | 14.2                   | 2.71 | 7,417   | 16.7                     | 2.50 | 14.0                   | 2.46 | 14.2                   | 2.65 |
| 11    | 3,987  | 17.5                     | 2.69 | 13.4                   | 3.67 | 12.9                   | 4.00 | 4,078   | 17.5                     | 2.92 | 13.4                   | 3.67 | 12.9                   | 4.04 |
| 12    | 6,760  | 17.6                     | 2.69 | 13.8                   | 2.78 | 13.8                   | 3.13 | 7,023   | 17.7                     | 2.73 | 13.7                   | 2.79 | 13.8                   | 3.18 |
| 13    | 3,111  | 18.6                     | 3.04 | 14.3                   | 2.87 | 14.2                   | 3.07 | 3,436   | 18.7                     | 3.03 | 14.2                   | 2.81 | 14.2                   | 3.00 |
| 14    | 5,447  | 19.3                     | 2.94 | 13.3                   | 3.59 | 12.9                   | 3.95 | 6,121   | 19.5                     | 3.02 | 13.3                   | 3.48 | 12.9                   | 3.90 |
| 15    | 3,278  | 20.0                     | 3.28 | 14.3                   | 2.85 | 14.3                   | 3.02 | 3,603   | 20.1                     | 3.16 | 14.2                   | 2.68 | 14.2                   | 2.93 |
| 16    | 3,948  | 20.8                     | 3.08 | 13.2                   | 3.19 | 13.3                   | 3.32 | 4,616   | 20.6                     | 2.96 | 13.2                   | 3.07 | 13.2                   | 3.24 |
| 17    | 5,468  | 21.3                     | 2.91 | 13.0                   | 3.36 | 12.8                   | 3.59 | 6,140   | 20.9                     | 2.95 | 13.2                   | 3.14 | 13.0                   | 3.44 |
| 18    | 4,224  | 21.8                     | 2.98 | 12.0                   | 3.60 | 11.7                   | 4.10 | 3,775   | 21.2                     | 3.12 | 12.7                   | 3.35 | 12.5                   | 3.74 |
| 19    | 2,664  | 22.0                     | 2.88 | 12.3                   | 3.04 | 12.4                   | 3.46 | 3,198   | 21.5                     | 3.28 | 13.0                   | 2.78 | 13.3                   | 3.03 |
| 20-29 | 10,005 | 23.3                     | 3.26 | 12.0                   | 3.53 | 11.9                   | 3.91 | 12,096  | 22.2                     | 3.77 | 12.5                   | 3.30 | 12.6                   | 3.62 |
| 30-39 | 7,952  | 25.0                     | 3.45 | 11.8                   | 2.93 | 12.0                   | 3.37 | 11,204  | 23.1                     | 4.18 | 11.9                   | 2.99 | 12.2                   | 3.35 |
| 40-49 | 9,440  | 25.7                     | 3.40 | 11.2                   | 3.22 | 11.0                   | 3.71 | 8,399   | 24.3                     | 4.48 | 11.7                   | 3.00 | 11.7                   | 3.38 |
| 50-59 | 4,720  | 26.7                     | 3.91 | 11.0                   | 3.11 | 10.6                   | 3.54 | 3,274   | 24.8                     | 4.40 | 10.8                   | 3.30 | 10.8                   | 3.41 |
| 60-69 | 4,397  | 26.2                     | 3.54 | 10.4                   | 3.24 | 10.0                   | 3.63 | 2,315   | 24.5                     | 3.90 | 10.3                   | 3.17 | 10.3                   | 3.57 |
| 70-79 | 2,187  | 25.6                     | 3.17 | 10.4                   | 3.40 | 9.8                    | 3.88 | 806     | 24.2                     | 3.93 | 10.0                   | 3.26 | 10.4                   | 3.79 |

Data from the following twin projects have been pooled: Europe (Child and Adolescent Twin Study in Sweden, Netherlands Twin Cohort of Children, FinnTwin12, FinnTwin16, East Flanders Prospective Twin Survey, Gemini, Italian Twin Registry, Norwegian Twin Registry, Portugal Twin Cohort, Twin Study of Child and Adolescent Development, Turkish Twin Study); United States (Boston University Twin Project, California Twin Program, Carolina African American Twin Study of Aging, Colorado Twin Registry, Michigan Twins Study, Mid-Atlantic Twin Registry, Minnesota Twin Registry, University of Southern California Twin Study, Texas Twin Project, Vietnam Era Twin Study of Aging, National Academy of Sciences National Research Council Study); East Asia (Korean Twin-Family Register, Ochanomizu University Twin Project, Qingdao Twin Registry Children, South Korea Twin Registry, West Japan Twins and Higher Order Multiple Births Registry); and others (Australian Twin Registry, Longitudinal Israeli Study of Twins).

As we reported previously, slightly higher variances of BMI were found from 6 to 12 years of age in DZ twins compared with MZ twins (20). However, these differences were minor (i.e., 15% or less) and became statistically significant only because of our very large sample size.

As we have previously reported for children (2) and adults (3), there was little evidence for the presence of dominance genetic variation in BMI. Thus, we used the additive genetic/shared environment/unique environment (ACE) model, which was also supported by the within-pair correlations in all parental education categories in our study cohort (Supporting Information Table S1), in the analyses. We fitted the full model in each age group to get the estimation of the role of shared environmental factors, even when it was not statistically significant in most of the age categories. A clear sex-specific genetic effect for BMI was found in childhood (2) and adulthood (3), and thus all models were fitted to allow the opposite-sex DZ genetic correlation to be lower than the 0.5 expected for same-sex DZ twins.

Especially in early childhood, DZ twins were slightly heavier than MZ twins (20), and thus a different mean BMI was used for MZ and DZ twins.

Next, we fitted gene environment interaction models to test the significance of the moderator effect of parental education (21). In these models, parental education, used as a continuous variable, was allowed to modify the genetic and environmental variation of BMI. Because weak but systematic shared environmental effects were found for BMI in this database, especially in childhood (2), we fitted both a more parsimonious additive genetic/unique environment model and an ACE model, which needs more statistical power. The genetic models were fitted to the data by the OpenMx package (version 2.0.1) of R statistical software (R Foundation, Vienna, Austria) (22). The effects of parental education on mean BMI were estimated by Stata/SE version 13.1 for Windows statistical software (StataCorp LLC, College Station, Texas). The effect of intrapair correlations on 95% confidence intervals (CIs) was taken into account by the cluster



option of Stata. Further, we adjusted these mean modification effects for zygosity because of slight differences in BMI (20) and parental education between MZ and DZ twins (17).

## Results

Table 1 presents the descriptive statistics by age and sex. Mean BMI shows the nadir at 5 years of age and the steady increase until 50 to 59 years of age with modest sex differences. Mean BMI was highest in North America and Australia and lowest in East Asia (Supporting Information Table S2). Maternal and paternal education decreased from the younger to the older age groups, reflecting the increasing levels of education over the birth cohorts. As expected, parental education was virtually identical for males and females.

Figure 1 presents the associations between parental education and BMI. No inverse educational association was seen from 1 to 3 years of age, and the sons of better-educated parents had even a slightly higher BMI. An inverse educational association emerged at 5 years of age in boys and 4 years of age in girls and became stronger until adolescence. In adulthood, the inverse association between parental education and BMI was statistically significant in most of the age groups and stronger in women than in men. In men, this association was somewhat weaker in late adulthood as compared with middle age, but otherwise no systematic differences between the age groups in adulthood were seen.

Figure 2 presents the associations between parental education and BMI in the three cultural-geographic regions. Because most of the BMI measures came from European cohorts, the pattern in Europe followed closely the estimates in the pooled cohort. In North America and Australia, parental education showed stronger associations with mean BMI than in Europe in most of age groups. These differences were more pronounced in females than in males. In East Asia, similar associations were found in females, but because of wider 95% CIs, they were not statistically significant. However, East Asian males showed no evidence for the association between parental education and BMI.

The total variation of BMI in the three categories of parental education, decomposed to additive genetic, shared environmental, and unique environmental variances, is shown in Figure 3 (the exact estimates with 95% CIs are provided in Supporting Information Table S3). The total BMI variation was greatest in the low parental education level category and smallest in the high parental education level category in all age groups. With a few exceptions, the BMI variation in the intermediate parental education level category was between the high and low education level categories. In nearly all age groups, the difference in BMI variation between the low and high parental education level categories was statistically significant, as seen by nonoverlapping 95% CIs (Supporting Information Table S3). When we studied the components of variation, a similar pattern was observed with a few exceptions for additive genetic and unique environmental variances. Except in two age groups, the difference was statistically significant for additive genetic variation, but for unique environmental variation, in nearly half of the age groups, the 95% CIs overlapped. Shared environmental variance components explained part of the variance, especially in boys and girls of 14 years of age or younger. However, in most of the age groups, they were not statistically significant, and the 95% CIs also overlapped between the educational categories (Supporting Information Table S3).

The gene-environment interaction models confirmed the results of the stratified analyses (Supporting Information Table S4). When we fitted the additive genetic/unique environment model, in all age groups except for 70- to 79-year-old men, additive genetic modification effects were negative (i.e., higher parental education level was associated with less genetic variation). However, in men 17 years of age or older, girls 3 years of age or younger, and women 50 to 59 years of age or older, the modification effects were weaker than in the other age groups and not significant. Most of the unique environmental modification effects were also negative but were weaker than additive genetic modification effects, and around half of them were not statistically significant. In the ACE model, most of the additive genetic and shared environmental modification effects were negative, but there was more fluctuation in the estimates because of lesser statistical power, and only some of them were statistically significant.

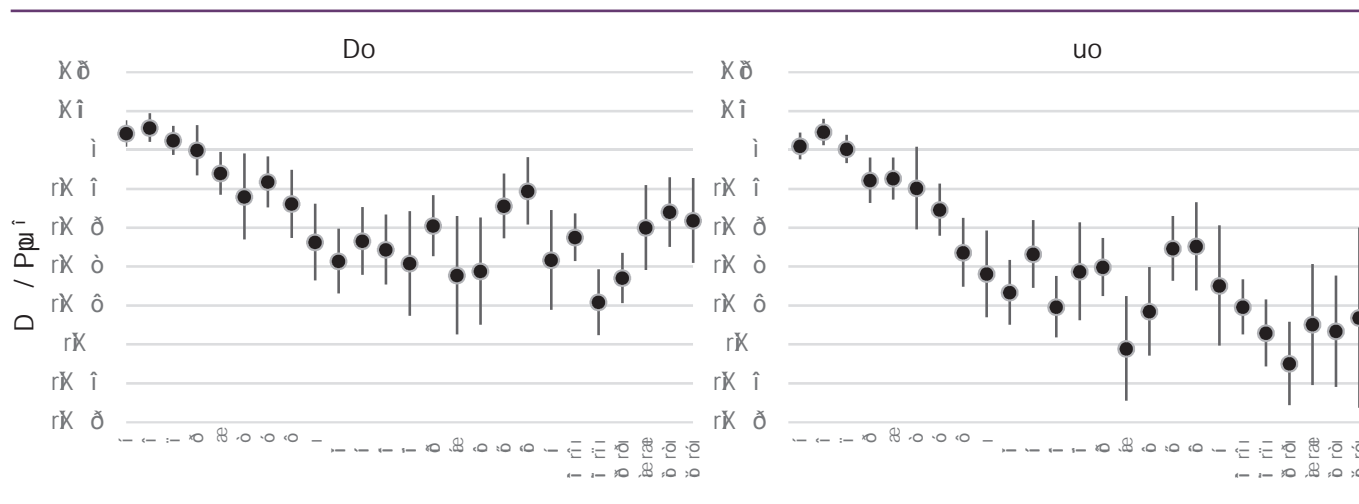
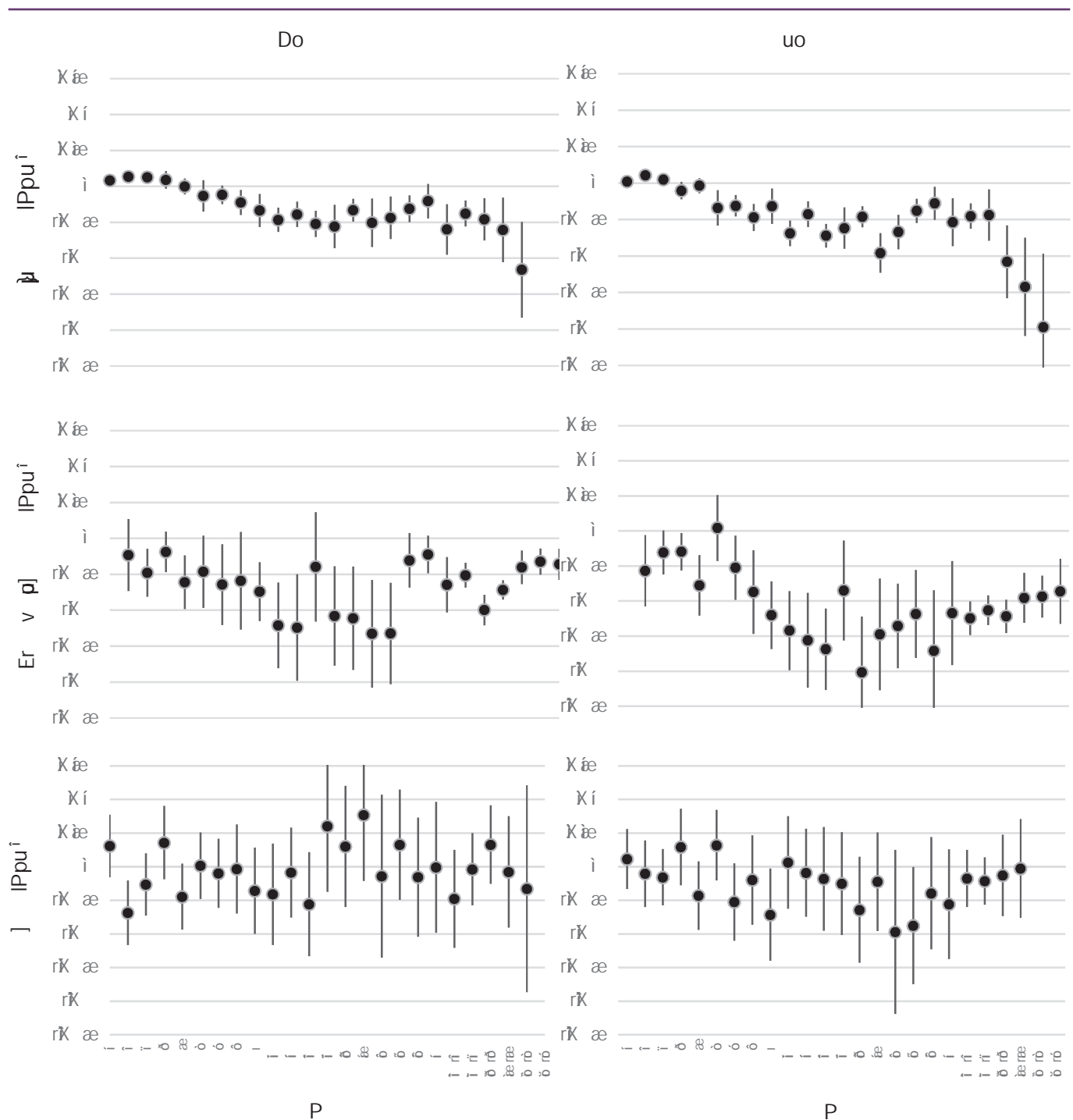


Figure 1 Mean BMI modification effects of parental education with 95% confidence intervals from 1 until 70 to 79 years of age by sex.



**Figure 2** Mean BMI modification effects of parental education with 95% confidence intervals from 1 until 70 to 79 years of age by sex and cultural-geographic region.

Figures 4 and 5 depict the similar decomposition of BMI variance by the cultural-geographic region. Because the results for the intermediate parental education level category were, in general, between the high and low education level categories, they are not shown, but all estimates with 95% CIs are available in Supporting Information Tables S5-S6. The total BMI variance was greatest in North America and

Australia and smallest in East Asia. In Europe, as well as in North America and Australia, BMI variation was systematically greater in males and females whose parents had low education levels as compared with the offspring of highly educated parents. In most of the age groups, this difference was statistically significant, as seen in the nonoverlapping 95% CIs (Supporting Information Tables S5-S6).

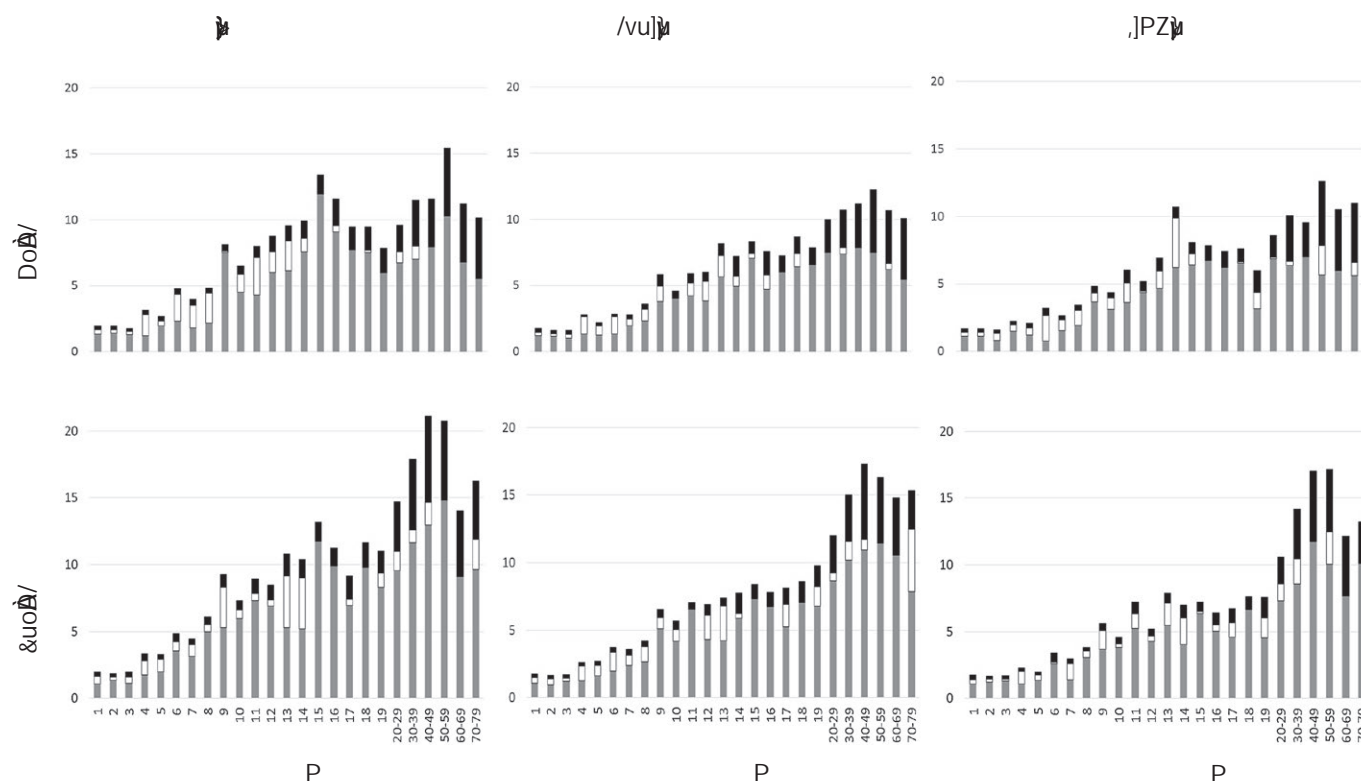


Figure 3 Total variation of BMI decomposed to additive genetic (gray), shared environmental (white), and unique environmental variations (black) from 1 until 70 to 79 years of age by sex and parental education.

When we restricted the analyses to North Americans and Australians with Caucasian ethnicity, the variances decreased somewhat, but they were still larger than in the other cultural-geographic regions and highest in those with low parental education levels (Supporting Information Tables S5-S6).

The differences in the total BMI variation between the parental educational categories were mainly due to differences in additive genetic variation. An exception was North American and Australian boys and girls 11 years of age or younger, for whom the difference in most age groups was mainly due to shared environmental variation. In Europe, we also observed some evidence for the greater role of shared environment in the low parental education level category until 14 years of age, but the differences were not statistically significant. In East Asia, no systematic differences were seen in the total variance of BMI according to parental education.

The gene environment interaction models confirmed these results (Supporting Information Table S7). In Europe, the additive genetic modification effects were consistently negative, whereas there was more fluctuation in the common environmental modifications effects. In contrast, in North America and Australia, especially in boys under 12 years of age, the shared environmental modifications were consistently negative. However, when using the ACE models, which require more statistical power, only some of these modification effects were statistically significant. In East Asia, the modification

effects fluctuated on both sides of zero, and most of them were not statistically significant.

## Discussion

In this study of a very large international data set of twins, we found that higher levels of parental education were consistently associated with lower additive genetic and unique environmental variance of BMI. This result is in accordance with previous twin and molecular genetic studies. In a previous study based on Dutch twin data, children and adolescents whose parents had moderate or low levels of education showed greater genetic BMI variance than those whose parents had high levels of education (3). Danish (12) and US (13) studies of adult twins supported this result by showing greater genetic variation in those with lower education levels than in those with higher education levels. These results are also in line with candidate genes studies in which the effects of low levels of maternal education on children (23) and of one's own education on adults (24) reinforced the effect of FTO gene, the major candidate gene of BMI. Similar results were found for other BMI candidate genes (25,26). However, these molecular genetic studies need replications in other populations, and, preferably, a GWA study using a large sample size should be conducted. Assuming parental education to be a good proxy indicator of the socioeconomic conditions of individuals and their families, our results might indicate that a poorer childhood socioeconomic environment reinforces the influence



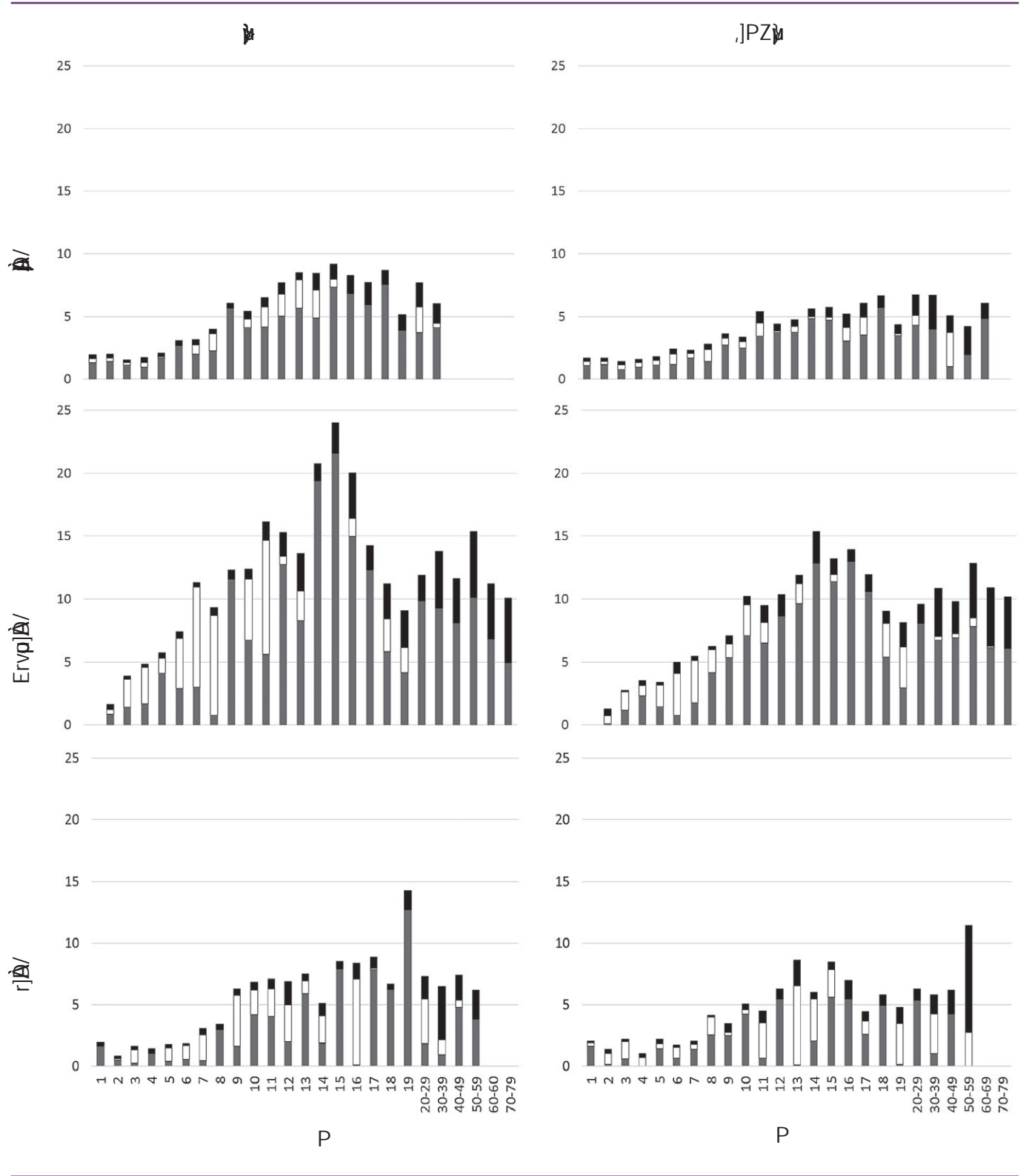


Figure 4 Total variation of BMI decomposed to additive genetic (gray), shared environmental (white), and unique environmental variations (black) from 1 until 70 to 79 years of age by parental education and geographic-cultural region in males.

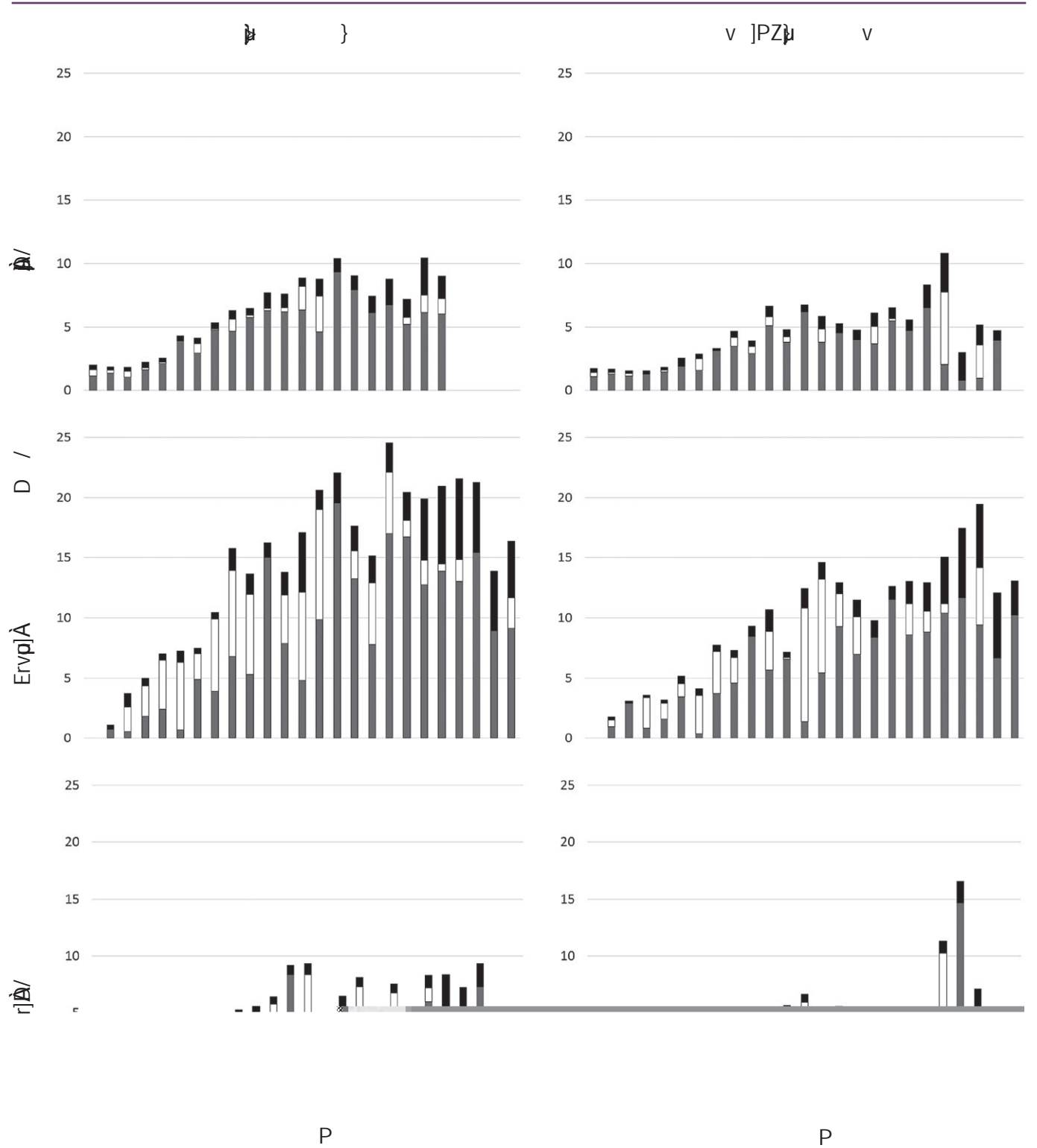


Figure 5 Total variation of BMI decomposed to additive genetic (gray), shared environmental (white), and unique environmental variations (black) from 1 until 70 to 79 years of age by parental education and geographic-cultural region in females.



